What is Claimed is:

1. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide derivative to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide derivative is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

2. A method according to Claim 1, wherein the oral administration of the effective amount of the insulin polypeptide derivative provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

3. A method according to Claim 1, wherein the effective amount of the insulin polypeptide derivative is between about 0.05 and about 10 mg per kilogram body weight.

4. A method according to Claim 1, wherein the oral administration of the effective amount of the insulin polypeptide derivative provides a maximum insulin drug concentration in peripheral blood within about 60 minutes.

5. A method according to Claim 1, wherein the oral administration of the effective amount of the insulin polypeptide derivative stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

6. A method according to Claim 1, wherein the insulin polypeptide derivative clears the bloodstream of the patient within about 4 hours following administration.

7. A method according to Claim 1, wherein the administration of the effective amount of the insulin polypeptide derivative reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

8. A method according to Claim 7, wherein the reduction in hepatic glucose production occurs within about 90 minutes of administration.

9. A method according to Claim 1, wherein the insulin polypeptide derivative is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal.

10. A method according to Claim 1, wherein the insulin polypeptide derivative is orally administered less than about one hour prior to ingestion of a meal by the patient.

11. A method according to Claim 1, wherein the insulin polypeptide derivative is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

12. A method according to Claim 1, wherein the insulin polypeptide derivative is orally administered less than about one hour after ingestion of a meal by the patient.

13. A method according to Claim 1, wherein the insulin polypeptide in the insulin polypeptide derivative is insulin.

14. A method according to Claim 1, wherein the insulin polypeptide derivative is an insulin polypeptide-oligomer conjugate.

15. A method according to Claim 14, wherein the insulin polypeptide-oligomer conjugate is an amphiphilically balanced insulin polypeptide-oligomer conjugate.

16. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an amphiphilically-balanced insulin polypeptide-oligomer conjugate to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

17. A method according to Claim 16, wherein the oral administration of the effective amount of the amphiphilically balanced insulin polypeptide-oligomer conjugate provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

18. A method according to Claim 16, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is between about 0.05 and about 10 mg per kilogram body weight.

19. A method according to Claim 16, wherein the oral administration of the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate provides a maximum insulin drug concentration in peripheral blood within about 60 minutes.

20. A method according to Claim 16, wherein the oral administration of the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

21. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate clears the bloodstream of the patient within about 4 hours following administration.

22. A method according to Claim 16, wherein the administration of the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

23. A method according to Claim 22, wherein the reduction in hepatic glucose production occurs within about 90 minutes of administration.

24. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal.

25. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate is orally administered less than about one hour prior to ingestion of a meal by the patient.

26. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

27. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate is orally administered less than about one hour after ingestion of a meal by the patient.

28. A method according to Claim 16, wherein the insulin polypeptide is insulin.

29. A method according to Claim 28, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

30. A method according to Claim 16, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin,

human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; Ala^{B28} Pro^{B29} insulin, human.

31. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide oligomer conjugate is present as a substantially monodispersed mixture.

32. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate is present as a monodispersed mixture.

33. A method according to Claim 16, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is present in a pharmaceutical composition.

34. A method according to Claim 16, wherein the amphiphilically-balanced insulin polypeptide-oligomer conjugate comprises a hydrophilic moiety and a lipophilic moiety.

35. A method according to Claim 34, wherein the hydrophilic moiety is a polyalkylene glycol moiety.

36. A method according to Claim 34, wherein the polyalkylene glycol moiety is a polyethylene glycol moiety.

37. A method according to Claim 34, wherein the polyalkylene glycol moiety has between 1 and 50 polyalkylene glycol subunits.

38. A method according to Claim 34, wherein the polyalkylene glycol moiety has between 3 and 50 polyalkylene glycol subunits.

39. A method according to Claim 34, wherein the polyalkylene glycol moiety has between 2 and 10 polyalkylene glycol subunits.

40. A method according to Claim 34, wherein the polyalkylene glycol moiety has between 4 and 10 polyalkylene glycol subunits.

41. A method according to Claim 34, wherein the polyalkylene glycol moiety has at least 2 polyalkylene glycol subunits.

42. A method according to Claim 34, wherein the lipophilic moiety is an alkyl or fatty acid moiety.

43. A method according to Claim 34, wherein the lipophilic moiety has between 1 and 28 carbon atoms.

44. A method according to Claim 34, wherein the lipophilic moiety has between 2 and 24 carbon atoms.

45. A method according to Claim 34, wherein the lipophilic moiety has between 3 and 18 carbon atoms.

46. A method according to Claim 34, wherein the lipophilic moiety has between 4 and 12 carbon atoms.

47. A method according to Claim 34, wherein the lipophilic moiety has between 5 and 7 carbon atoms.

48. A method according to Claim 34, wherein the lipophilic moiety has between 4 and 14 carbon atoms.

49. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula I:

Insulin Polypeptide—B—L_j—G_k—R—G'_m—R'—G''_n—T (I)

wherein:

B is a bonding moiety;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety; and

j, k, m and n are individually 0 or 1;

to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the conjugate of Formula I is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

50. A method according to Claim 49, wherein the oral administration of the effective amount of the conjugate of Formula I provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

51. A method according to Claim 49, wherein the effective amount of the conjugate of Formula I is between about 0.05 and 10 mg per kilogram body weight.

52. A method according to Claim 49, wherein the oral administration of the effective amount of the conjugate of Formula I provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

53. A method according to Claim 49, wherein the oral administration of the effective amount of the conjugate of Formula I stabilizes peripheral glucose concentration to

within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

54. A method according to Claim 49, wherein the conjugate of Formula I clears the bloodstream of the patient within about 4 hours following administration.

55. A method according to Claim 49, wherein the administration of the effective amount of the conjugate of Formula I reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

56. A method according to Claim 55, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

57. A method according to Claim 49, wherein the conjugate of Formula I is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal.

58. A method according to Claim 49, wherein the conjugate of Formula I is orally administered less than about one hour prior to ingestion of a meal by the patient.

59. A method according to Claim 49, wherein the conjugate of Formula I is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

60. A method according to Claim 49, wherein the conjugate of Formula I is orally administered less than about one hour after ingestion of a meal by the patient.

61. A method according to Claim 49, wherein the insulin polypeptide is insulin.

62. A method according to Claim 61, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

63. A method according to Claim 49, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; Ala^{B28} Pro^{B29} insulin, human.

64. A method according to Claim 49, wherein the conjugate of Formula I is present as a substantially monodispersed mixture.

65. A method according to Claim 49, wherein the conjugate of Formula I is present as a monodispersed mixture.

66. A method according to Claim 49, wherein the conjugate of Formula I is amphiphilically balanced.

67. A method according to Claim 49, wherein the effective amount of the conjugate of Formula I is present in a pharmaceutical composition.

68. A method according to Claim 49, wherein B is selected from the group consisting of an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety and a covalent bond.

69. A method according to Claim 49, wherein L is selected from the group consisting of alkyl moieties and fatty acid moieties.

70. A method according to Claim 49, wherein G, G' and G" are individually selected from the group consisting of sugar moieties, cholesterol, and glycerine moieties.

71. A method according to Claim 49, wherein T is selected from the group consisting of alkyl and alkoxy.

72. A method according to Claim 49, wherein the polyalkylene glycol moiety is a polyethylene glycol moiety.

73. A method according to Claim 72, wherein the polyethylene glycol moiety has between 1 and 50 polyethylene glycol subunits.

74. A method according to Claim 72, wherein the polyethylene glycol moiety has between 3 and 50 polyethylene glycol subunits.

75. A method according to Claim 72, wherein the polyethylene glycol moiety has between 2 and 10 polyethylene glycol subunits.

76. A method according to Claim 72, wherein the polyethylene glycol moiety has between 4 and 10 polyethylene glycol subunits.

77. A method according to Claim 72, wherein the polyethylene glycol moiety has at least 2 polyethylene glycol subunits.

78. A method according to Claim 49, wherein the lipophilic moiety is an alkyl or a fatty acid moiety.

79. A method according to Claim 78, wherein the lipophilic moiety has between 1 and 28 carbon atoms.

80. A method according to Claim 78, wherein the lipophilic moiety has between 2 and 24 carbon atoms.

81. A method according to Claim 78, wherein the lipophilic moiety has between 3 and 18 carbon atoms.

82. A method according to Claim 78, wherein the lipophilic moiety has between 4 and 12 carbon atoms.

83. A method according to Claim 78, wherein the lipophilic moiety has between 5 and 7 carbon atoms.

84. A method according to Claim 78, wherein the lipophilic moiety has between 4 and 14 carbon atoms.

85. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula II:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_mY(C_2H_4O)_nR \qquad \text{(II)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety or a covalent bond;

Y is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the conjugate of Formula II is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

86. A method according to Claim 85, wherein the oral administration of the effective amount of the conjugate of Formula II provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

87. A method according to Claim 85, wherein the effective amount of the conjugate of Formula II is between about 0.05 and 10 mg per kilogram body weight.

88. A method according to Claim 85, wherein the oral administration of the effective amount of the conjugate of Formula II provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

89. A method according to Claim 85, wherein the oral administration of the effective amount of the conjugate of Formula II stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

90. A method according to Claim 85, wherein the conjugate of Formula II clears the bloodstream of the patient within about 4 hours following administration.

91. A method according to Claim 85, wherein the administration of the effective amount of the conjugate of Formula II reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

92. A method according to Claim 91, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

93. A method according to Claim 85, wherein the conjugate of Formula II is orally administered such that at least about 25 percent of post-prandial glucose resulting from

ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the patient.

94. A method according to Claim 85, wherein the conjugate of Formula II is orally administered less than about one hour prior to ingestion of a meal by the patient.

95. A method according to Claim 85, wherein the conjugate of Formula II is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

96. A method according to Claim 85, wherein the conjugate of Formula II is orally administered less than one about hour after ingestion of a meal by the patient.

97. A method according to Claim 85, wherein the insulin polypeptide is insulin.

98. A method according to Claim 97, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

99. A method according to Claim 85, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; Ala^{B28} Pro^{B29} insulin, human.

100. A method according to Claim 85, wherein the conjugate of Formula II is present as a substantially monodispersed mixture.

101. A method according to Claim 85, wherein the conjugate of Formula II is present as a monodispersed mixture.

102. A method according to Claim 85, wherein the conjugate of Formula II is amphiphilically balanced.

103. A method according to Claim 85, wherein the effective amount of the conjugate of Formula II is present in a pharmaceutical composition.

104. A method according to Claim 85, wherein the polyalkylene glycol moiety is a polyethylene glycol moiety.

105. A method according to Claim 85, wherein m is between 3 and 16.

106. A method according to Claim 85, wherein m is between 4 and 14.

107. A method according to Claim 85, wherein m is between 5 and 10.

108. A method according to Claim 85, wherein n is between 3 and 18.

109. A method according to Claim 85, wherein n is between 4 and 14.

110. A method according to Claim 85, wherein n is between 5 and 10.

111. A method according to Claim 85, wherein R is lower alkyl.

112. A method according to Claim 85, wherein R is C_1 to C_3 alkyl.

113. A method according to Claim 85, wherein R is methyl.

114. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the conjugate of Formula III is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

115. A method according to Claim 114, wherein the oral administration of the effective amount of the conjugate of Formula III provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

116. A method according to Claim 114, wherein the effective amount of the conjugate of Formula III is between about 0.05 and 10 mg per kilogram body weight.

117. A method according to Claim 114, wherein the oral administration of the effective amount of the conjugate of Formula III provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

118. A method according to Claim 114, wherein the oral administration of the effective amount of the conjugate of Formula III stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

119. A method according to Claim 114, wherein the conjugate of Formula III clears the bloodstream of the patient within about 4 hours following administration.

120. A method according to Claim 114, wherein the administration of the effective amount of the conjugate of Formula III reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

121. A method according to Claim 120, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

122. A method according to Claim 114, wherein the conjugate of Formula III is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the patient.

123. A method according to Claim 114, wherein the conjugate of Formula III is orally administered less than about one hour prior to ingestion of a meal by the patient.

124. A method according to Claim 114, wherein the conjugate of Formula III is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

125. A method according to Claim 114, wherein the conjugate of Formula III is orally administered less than about one hour after ingestion of a meal by the patient.

126. A method according to Claim 114, wherein the insulin polypeptide is insulin.

127. A method according to Claim 126, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

128. A method according to Claim 114, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human;

Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; Ala^{B28} Pro^{B29} insulin, human.

129. A method according to Claim 114, wherein the conjugate of Formula III is present as a substantially monodispersed mixture.

130. A method according to Claim 114, wherein the conjugate of Formula III is present as a monodispersed mixture.

131. A method according to Claim 114, wherein the conjugate of Formula III is amphiphilically balanced.

132. A method according to Claim 114, wherein the effective amount of the conjugate of Formula III is present in a pharmaceutical composition.

133. A method according to Claim 114, wherein m is between 3 and 16.

134. A method according to Claim 114, wherein m is between 4 and 14.

135. A method according to Claim 114, wherein m is between 5 and 10.

136. A method according to Claim 114, wherein n is between 3 and 18.

137. A method according to Claim 114, wherein n is between 4 and 14.

138. A method according to Claim 114, wherein n is between 5 and 10.

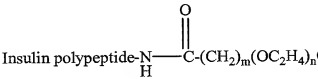
139. A method according to Claim 114, wherein R is lower alkyl.

140. A method according to Claim 114, wherein R is C_1 to C_3 alkyl.

141. A method according to Claim 114, wherein R is methyl.

142. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula IV:



$$\text{Insulin polypeptide-}\underset{\text{H}}{\text{N}}\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}(CH_2)_m(OC_2H_4)_nOR \qquad \text{(IV)}$$

wherein:

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the conjugate of Formula IV is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

143. A method according to Claim 142, wherein the oral administration of the effective amount of the conjugate of Formula IV provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

144. A method according to Claim 142, wherein the effective amount of the conjugate of Formula IV is between about 0.05 and about 10 mg per kilogram body weight.

145. A method according to Claim 142, wherein the oral administration of the effective amount of the conjugate of Formula IV provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

146. A method according to Claim 142, wherein the oral administration of the effective amount of the conjugate of Formula IV stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

147. A method according to Claim 142, wherein the conjugate of Formula IV clears the bloodstream of the patient within about 4 hours following administration.

148. A method according to Claim 142, wherein the administration of the effective amount of the conjugate of Formula IV reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

149. A method according to Claim 148, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

150. A method according to Claim 142, wherein the conjugate of Formula IV is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the patient.

151. A method according to Claim 142, wherein the conjugate of Formula IV is orally administered less than about one hour prior to ingestion of a meal by the patient.

152. A method according to Claim 142, wherein the conjugate of Formula IV is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

153. A method according to Claim 142, wherein the conjugate of Formula IV is orally administered less than about one hour after ingestion of a meal by the patient.

154. A method according to Claim 142, wherein the insulin polypeptide is insulin.

155. A method according to Claim 154, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

156. A method according to Claim 142, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; Ala^{B28} Pro^{B29} insulin, human.

157. A method according to Claim 142, wherein the conjugate of Formula IV is present as a substantially monodispersed mixture.

158. A method according to Claim 142, wherein the conjugate of Formula IV is present as a monodispersed mixture.

159. A method according to Claim 142, wherein the conjugate of Formula IV is amphiphilically balanced.

160. A method according to Claim 142, wherein the effective amount of the conjugate of Formula IV is present in a pharmaceutical composition.

161. A method according to Claim 142, wherein m is between 3 and 16.

162. A method according to Claim 142, wherein m is between 4 and 14.

163. A method according to Claim 142, wherein m is between 5 and 10.

164. A method according to Claim 142, wherein n is between 3 and 18.

165. A method according to Claim 142, wherein n is between 4 and 14.

166. A method according to Claim 142, wherein n is between 5 and 10.

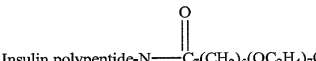
167. A method according to Claim 142, wherein R is lower alkyl.

168. A method according to Claim 142, wherein R is C_1 to C_3 alkyl.

169. A method according to Claim 142, wherein R is methyl.

170. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula V:



$$\text{Insulin polypeptide-}\underset{\text{H}}{\text{N}}\text{---}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-}(CH_2)_5(OC_2H_4)_7OCH_3 \qquad \text{(V)}$$

to the patient within one hour of ingestion of a meal by the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the conjugate of Formula V is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

171. A method according to Claim 170, wherein the oral administration of the effective amount of the conjugate of Formula V provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

172. A method according to Claim 170, wherein the effective amount of the conjugate of Formula V is between about 0.05 and 10 mg per kilogram body weight.

173. A method according to Claim 170, wherein the oral administration of the effective amount of the conjugate of Formula V provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

174. A method according to Claim 170, wherein the oral administration of the effective amount of the conjugate of Formula V stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

175. A method according to Claim 170, wherein the conjugate of Formula V clears the bloodstream of the patient within about 4 hours following administration.

176. A method according to Claim 170, wherein the administration of the effective amount of the conjugate of Formula V reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

177. A method according to Claim 176, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

178. A method according to Claim 170, wherein the conjugate of Formula V is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the patient.

179. A method according to Claim 170, wherein the conjugate of Formula V is orally administered less than about one hour prior to ingestion of a meal by the patient.

180. A method according to Claim 170, wherein the conjugate of Formula V is orally administered substantially contemporaneously with the ingestion of a meal by the patient.

181. A method according to Claim 170, wherein the conjugate of Formula V is orally administered less than about one hour after ingestion of a meal by the patient.

182. A method according to Claim 170, wherein the insulin polypeptide is insulin.

183. A method according to Claim 182, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

184. A method according to Claim 170, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; Ala^{B28} Pro^{B29} insulin, human.

185. A method according to Claim 170, wherein the conjugate of Formula V is present as a substantially monodispersed mixture.

186. A method according to Claim 170, wherein the conjugate of Formula V is present as a monodispersed mixture.

187. A method according to Claim 170, wherein the effective amount of the conjugate of Formula V is present in a pharmaceutical composition.

188. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide derivative to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide derivative is administered so that it provides an insulin drug concentration

in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

189. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide derivative to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide derivative is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

190. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide derivative to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide derivative is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

191. A method according to Claim 190, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

192. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide derivative to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide derivative is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the patient.

193. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an amphiphilically-balanced insulin polypeptide-oligomer conjugate to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and about 1,000 U/ml within about 60 minutes of administration.

194. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an amphiphilically-balanced insulin polypeptide-oligomer conjugate to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

195. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an amphiphilically-balanced insulin polypeptide-oligomer conjugate to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

196. A method according to Claim 195, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

197. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an amphiphilically-balanced insulin polypeptide-oligomer conjugate to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes of ingestion of the meal by the patient.

198. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula I:

$$\text{Insulin Polypeptide}—B—L_j—G_k—R—G'_m—R'—G''_n—T \qquad (I)$$

wherein:

B is a bonding moiety selected from the group consisting of an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety and a covalent bond;

L is a linker moiety selected from the group consisting of alkyl moieties and fatty acid moieties;

G, G' and G" are spacer moieties individually selected from the group consisting of sugar moieties, cholesterol, and glycerine moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety selected from the group consisting of alkyl and alkoxy; and

j, k, m and n are individually 0 or 1;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

199. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula I:

$$\text{Insulin Polypeptide}—B—L_j—G_k—R—G'_m—R'—G''_n—T \qquad (I)$$

wherein:

B is a bonding moiety selected from the group consisting of an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, and a covalent bond;

L is a linker moiety selected from the group consisting of alkyl moieties and fatty acid moieties;

G, G' and G" are spacer moieties individually selected from the group consisting of sugar moieties, cholesterol, and glycerine moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety selected from the group consisting of alkyl and alkoxy; and

j, k, m and n are individually 0 or 1;

to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

200. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula I:

$$\text{Insulin Polypeptide}—B—L_j—G_k—R—G'_m—R'—G''_n—T \qquad (I)$$

wherein:

B is a bonding moiety selected from the group consisting of an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, and a covalent bond;

L is a linker moiety selected from the group consisting of alkyl moieties and fatty acid moieties;

G, G' and G" are spacer moieties individually selected from the group consisting of sugar moieties, cholesterol, and glycerine moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety selected from the group consisting of alkyl and alkoxy; and

j, k, m and n are individually 0 or 1;

to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

201. A method according to Claim 200, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

202. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula I:

$$\text{Insulin Polypeptide}—B—L_j—G_k—R—G'_m—R'—G''_n—T \qquad (I)$$

wherein:

B is a bonding moiety selected from the group consisting of an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, and a covalent bond;

L is a linker moiety selected from the group consisting of alkyl moieties and fatty acid moieties;

G, G' and G" are spacer moieties individually selected from the group consisting of sugar moieties, cholesterol, and glycerine moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety selected from the group consisting of alkyl and alkoxy; and

j, k, m and n are individually 0 or 1;

to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes of ingestion of the meal by the patient.

203. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula II:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_mY(C_2H_4O)_nR \qquad \text{(II)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

Y is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

204. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula II:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_mY(C_2H_4O)_nR \qquad \text{(II)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

Y is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

205. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula II:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_mY(C_2H_4O)_nR \qquad \text{(II)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

Y is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

206. A method according to Claim 205, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

207. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of an insulin polypeptide-oligomer conjugate comprising the structure of Formula II:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_mY(C_2H_4O)_nR \qquad \text{(II)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

Y is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes of ingestion of the meal by the patient.

208. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

209. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average

peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

210. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

211. A method according to Claim 210, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

212. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:

X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes of ingestion of the meal by the patient.

213. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula IV:

$$\text{Insulin polypeptide-}\underset{\underset{H}{|}}{N}\text{-}\overset{\overset{O}{\|}}{C}\text{-}(CH_2)_m(OC_2H_4)_nOR \qquad \text{(IV)}$$

wherein:

m is between 1 and 24;

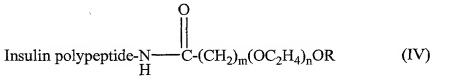
n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

214. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula IV:



Insulin polypeptide-N(H)-C(=O)-$(CH_2)_m(OC_2H_4)_nOR$ (IV)

wherein:

m is between 1 and 24;

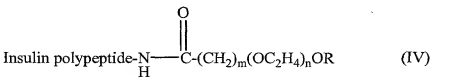
n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

215. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula IV:



Insulin polypeptide-N(H)-C(=O)-$(CH_2)_m(OC_2H_4)_nOR$ (IV)

wherein:

m is between 1 and 24;

n is between 1 and 50; and

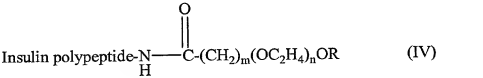
R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

216. A method according to Claim 215, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

217. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula IV:



$$\text{Insulin polypeptide-}\underset{\text{H}}{\text{N}}\text{—C(=O)-(CH}_2\text{)}_m\text{(OC}_2\text{H}_4\text{)}_n\text{OR} \qquad \text{(IV)}$$

wherein:

m is between 1 and 24;

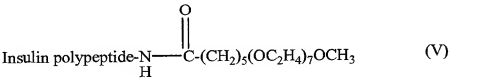
n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes of ingestion of the meal by the patient.

218. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula V:



$$\text{Insulin polypeptide-}\underset{\text{H}}{\text{N}}\text{—C(=O)-(CH}_2\text{)}_5\text{(OC}_2\text{H}_4\text{)}_7\text{OCH}_3 \qquad \text{(V)}$$

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that

it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

219. A method according to Claim 218, wherein the insulin polypeptide is insulin.

220. A method according to Claim 219, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

221. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula V:

Insulin polypeptide-N(H)—C(=O)-$(CH_2)_5(OC_2H_4)_7OCH_3$ (V)

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

222. A method according to Claim 221, wherein the insulin polypeptide is insulin.

223. A method according to Claim 222, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

224. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula V:

(V)

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the patient without administration.

225. A method according to Claim 224, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

226. A method according to Claim 224, wherein the insulin polypeptide is insulin.

227. A method according to Claim 226, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

228. A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula V:

(V)

to the patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the amphiphilically-balanced insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the patient.

229. A method according to Claim 228, wherein the insulin polypeptide is insulin.

230. A method according to Claim 229, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.